DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

JAN 30 2004

Date: _____ 6146 '04 FEB -4 P1:53

From: Interdisciplinary Scientist/Pharmacist , Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Nano Red Elemental Selenium

Firm: Nano Port (USA) Inc.

Date Received by FDA: 6/04/03

90-Day Date: 9/04/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Gloria Cheng

P drive/ NDI/ NDI File Closeout/DDSP SOP closeout process...

95S-0316

RPT 194

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administratio
College Park, MD 20740-38

AUG 19 2003

Mr. Har Fei, President
Nano Port (USA) Inc.
Suite 262
3380 Sheridan Drive
Amherst, New York 14226

Dear Mr. Yu Har Fei:

This is to inform you that the notification you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on June 4, 2003. Your notification concerns the substance, Nano Red Elemental Selenium under the trade name of Nano-Se, that you intend to market as a new dietary ingredient.

The description of your substance states that the level of the new dietary ingredient within a supplement will be 45 micrograms (mcg) of selenium (Nano Red Elemental Selenium) in each capsule. The conditions of use are to take one to two capsules 1 to 2 times daily or as directed by a health professional.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing Nano Red Elemental Selenium (Nano-Se) will reasonably be expected to b safe.

Inadequate information is provided about the chemical identity of the substance that is "Nano-Se." Because the submission does not provide the information that enables the substance that is the subject of the notification to be identified, it is not possible to determine whether the information contained in the submission provides an adequate basis to conclude that the dietary supplement will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling.

Most of the studies you referenced did not use your substance as the test article. In other studies you submitted, it was unclear whether the test substances used were qualitatively and quantitatively the same as your substance. Further, one referenced study that appeared to use your substance focused primarily on bioavailability and antioxidant effects and not on safety.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Nano Red Elemental Selenium (Nano-Se), when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such an ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of June 4, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

for Robert A Moore

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

NANO PORT (USA) INC.

3380 Sheridan Drive Suite 262 Amherst, NY 14226 U.S.A
Tel : 917-495-0644

May 20, 2003

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, 20740-3835

Dear Sir,

New Dietary Ingredient Notification: Nano-Se

Nano Port (U.S.A.) Inc would like to introduce into the health food market of Nano Red Elemental Selenium (under the trade name of Nano-Se), following the 75 days waiting periods as provided by Law.

1. Distributor's name and address:
NANO PORT (USA) INC.
3380 Sheridan Drive Suite
262 Amherst
NY 14226, U.S.A.

2. Name of dietary ingredient:
Nano red elemental selenium under the trade name Nano-Se

3. Description of the dietary supplement that contains the dietary ingredient:
Each bottle contains 72 capsules
Each capsule contains 45 mcg selenium (Nano red elemental selenium)
Other ingredients: Starch and dextrin
Suggested usage: Take one to two capsules 1 to 2 times daily or as directed by a health professional.

4. **Se and its Safety:**
Selenium (Se) is an essential trace element, it is metabolised within the human body into an array of selenoproteins: classical glutathione peroxidase (GPx1), gastrointestinal glutathione peroxidase (GPx2), extracellular glutathione peroxidase (GPx3), phospholipid hydroperoxide glutathione peroxidase (GPx4), thioredoxin reductase (TR1 and TR2), iodothyronine deiodinase (IDI, IIDI, and IIIDI), selenoprotein P, and selenoprotein W. It is well recognised that dietary selenium is

protective effect against some forms of cancer [1].

There are several selenocompounds in tissues of plants and animals. Selenate is the major inorganic selenocompound found in both animal and plant tissues. Selenocysteine is the predominant selenoamino acid in tissues when inorganic selenium is given to animals. Selenomethionine is the major selenocompound found initially in animal given this selenoamino acid, but is converted with time afterwards to selenocysteine. Selenomethionine is the major selenocompound in cereal grains, grassland legumes and soybeans. Se-methylselenocysteine is the major selenocompound in selenium enriched plants such as garlic, onions, broccoli florets and sprouts, and wild leeks. Sodium selenite is the major inorganic form for comparison of bioavailability and toxicity among different forms of Se [2, 3].

The typical American diet provides the average adult with about 80 to 150 mcg of Se per day, which is more than the newly revised RDA for selenium of 55 mcg, but less than one half of the amount considered optimal for utilization of the protective potential of Se, especially for cancer prevention. Accordingly, extra dietary selenium supplementation is increasingly recommended by health professionals. As to the safety of Se, a supplemental dose of 200 mcg per day would cause the total daily Se intake of an average adult to increase to 280 to 350 mcg. This is a safe amount since it is below or equal to the Reference Dose (RfD) for selenium, which, for an adult of 70 kg, was set by the EPA at 350 mcg [4,5]. The RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. In line with this definition, studies have shown that prolonged daily selenium intakes of 750 to 850 mcg do not produce adverse effects [4, 5]. Sodium selenite, sodium selenate, selenomthonine, seleno-yeast and methyselenocystein have been used for Se supplementaion at the dose equal to or below 200 mcg Se daily. Long-term consumption of seleno-yeast (200 mcg Se daily, mostly in the form of selenomethionine) in 1312 persons for 4.5 years showed no toxicity and revealed a significant reduction in lung, prostate and colorectal cancer [6].

5. Nano-Se and its safety:

The efficacy of Se in inducing Se-containing enzymes and the pro-oxidative effect are determined by its chemical form. Normally, gray and black bulk particle of elemental Se (Se^0) has neither biological activity nor toxicity. It is known that particles of Se^0 formed from some bacterial strains and the redox system of glutathione or ascorbate and selenite has a very low bioavailability [7-9].We observed that red elemental Se, formed in the redox system of selenite and GSH or other reducing agents, was unstable and could further aggregate into gray and black Se^0 if there were no

affect the aggregation of red Se^0. The resulting Se^0 was bright red, highly stable, soluble and of nano define size. Nano-Se was prepared by the reaction of bovine serum albumin (BSA), sodium selenite, and GSH under the Chinese Patent ZL97107038.5. The final solution containing Nano-Se and BSA. X-ray photoelectric energy spectra (XPS) showed the binding energy of Se 3d was 55.3 eV indicating Se^0. Transmission Electron Microscopy (TEM) showed the size of red elemental Se was between 20~60nm [10, 11].

The Nano-Se shows totally different biological properties contrasting to the general concepts that elemental Se is inert. In HepG2 cells, Both Nano-Se and selenite have almost equal biological functions in increase of glutathione peroxidase (GPx), phospholipid hydroperoxide glutathione peroxidase (PHGPx) and thioredoxin reductase (TR), protection against free racial-mediated damage, and cell growth inhibition. Nano-Se has a 7-fold lower acute toxicity than sodium selenite in mice (LD_{50} 113 and 15 mg Se/kg body weight respectively). In Se deficient rat, both Nano-Se and selenite were efficient and generally equal in Se uptake and GPx biosynthesis [10].

Other toxicity investigations of Nano-Se are shown in two attatchments, in general Nano-Se's subchronic toxicity is near to sodium selenite and Se-enriched soybean, however, sodium selenite and Se-enriched soybean at 6 ppm in diet caused more overt growth inhibition, haematology changes and transaminases release from liver compared with Nano-Se at the same Se dose in diet [attachment 1]. Although these observations could not lead to consider Nano-Se's subchronic toxicity is definitely lower than sodium selenite and Se-enriched soybean, however, it is safe to conclude that this novel form of Se is not more toxic compared with inorganic and natural occuring Se. An independent research using Nano-Se at 1, 3, and 6 ppm in diet for subchronic toxicity evaluation showed Nano-Se did not cause obvious growth inhibition, being consistent with the results in attachment1 [attachment2].

Nano-Se, taken at the dose of 180 mcg Se daily, was granted as health care food by Ministry of Hygiene P. R. China in 1998.

In summary, Nano-Se has comparable bioavailability of selenite, sharply lower acute toxicity, to less extent, lower subchronic toxicity at a dose therein other selenocompounds, such as selenite and Se-enriched soybean could cause serious toxic changes. Supplement at 180 mcg per day for adults is within the scope of RfD.

Dr. JS Zhang is our Research Scientist and would appreciate any comment you may have on the Nano-Se product prior to its introduce into the health food market.

NANO PORT (USA) INC.

3380 Sheridan Drive Suite 262 Amherst, NY 14226 U.S.A
Tel : 917-495-0644

6. Signature of the distributor of this dietary supplement.

NANO PORT (USA) INC.

By:

Yu Har Fei
President

Enclosures

Reference

1. KM Brown and JR Arthur. Selenium, selenoproteins and human health: a review. Public Health Nutrition: ***49:***593-599, 2001.
2. GF Combs Jr. Review article: selenium in global food systems. British Journal of Nutrition. ***85:***517-547, 2001.
3. PD Whanger. Review: selenocompounds in plants and animals and their biological significance. Journal of the American College of Nutrition. ***21:***223-232, 2002.
4. GN Schrauzer. Selenomethionine: A review of its nutritional significance, metabolism and toxicity. J. Nutr. ***130:***1653-1656, 2000.
5. GN Schrauzer. Commentary: Nutritional selenium supplements: product types, quality, and safety. Journal of the American College of Nutrition. ***20:***1-4, 2001.
6. LC Clark, GF Combs, BW Turnbull, EH Slate, DK Chalker, J Chow, LS Davis, RA Clover, GF Graham, EG Gross, A Krongrad, JL Lesher, HK Park, BB Sanders, CL Smith, and JR Taylor, Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin, J. Am. Med. Assoc. ***276:***1957-1963, 1996.
7. GF Combs, C Garbisu, BC Yee, A Yee, DE Carlson, NR Smith, AC Magyarosy, T Leighton and BB Buchanan. Bioavailability of selenium accumulated by selenite-reducing bacteria. Biol. Trace Elem. Res. ***52:***209-225, 1996.
8. C Garbisu, T Ishii, T Leighton and BB Buchanan. Bacterial reduction of selenite to elemental selenium. Chemical Geology. ***132:***199-204, 1996.
9. CE Schlekat, PR Dowdle, BG Lee, SN Luoma and RS Oremland. Bioavailability of particle-associated Se to the bivale potamocorbula amurensis. Env. Sci. & Techno. ***34:***4504-4510, 2000.
10. JS Zhang, XY Gao, LD Zhang, and YP Bao. Biological effects of a nano red elemental selenium. BioFactors. ***15:***27-38, 2001.
11. XY Gao, JS Zhang, and LD Zhang. Hollow sphere selenium nanoparticles: their in vitro anti hydroxyl radical effect. Adv. Mater. ***14:***290-293, 2002.

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Attachments

1. Report on toxicity test of Xiwang capsule
2. REPORT ON QUALITY TEST by Analytic and Testing Centre of Nanjing Railway Medical College